Appendix H: Data analysis

H.1 Review question 1 data analysis

No additional data analysis performed for this question

H.2 Review question 2 data analysis

No additional data analysis performed for this question

H.3 Review question 3 data analysis

No additional data analysis performed for this question

H.4 Review question 4 data analysis

No additional data analysis performed for this question

H.5 Review question 5 data analysis

No additional data analysis performed for this question

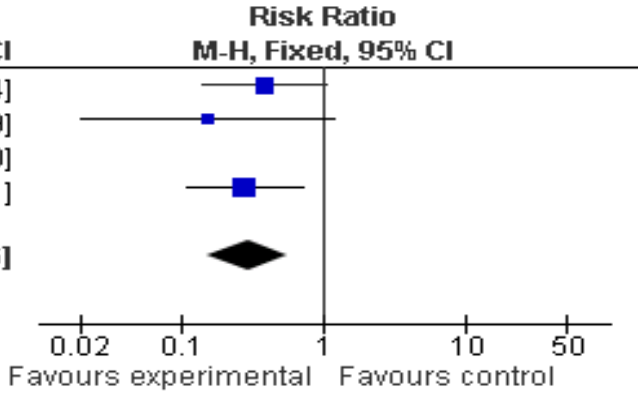
H.6 Review question 6 data analysis

H.6.1 Self-temperature monitoring for prevention of diabetic foot problems:

Rate of Ulceration

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Armstrong 2007	5	106	14	115	35.7%	0.39 [0.14, 1.04]
Lavery 2004	1	41	7	44	17.9%	0.15 [0.02, 1.19]
Lavery 2007	17	58	17	56	0.0%	0.97 [0.55, 1.70]
Lavery 2007	5	59	17	56	46.4%	0.28 [0.11, 0.71]
Total (95% CI)		**206**		**215**	**100.0%**	**0.30 [0.16, 0.56]**
Total events	11		38			

Heterogeneity: Chi² = 0.70, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 3.74 (P = 0.0002)

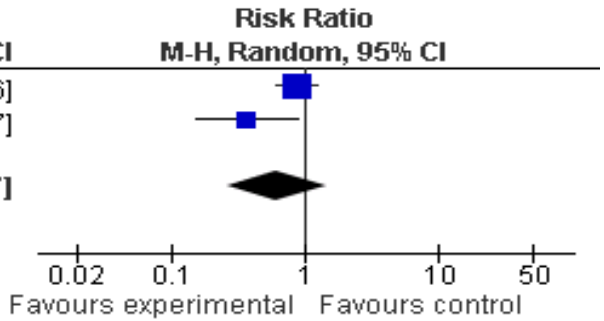


H.6.2 Pressure customised vs shape customised orthoses for prevention of diabetic foot problems amongst high risk patients:

Rate of Ulceration

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bus 2013	33	85	38	86	60.1%	0.88 [0.61, 1.26]
Ulbrecht 2014	6	66	16	64	39.9%	0.36 [0.15, 0.87]
Total (95% CI)		**151**		**150**	**100.0%**	**0.62 [0.26, 1.47]**
Total events	39		54			

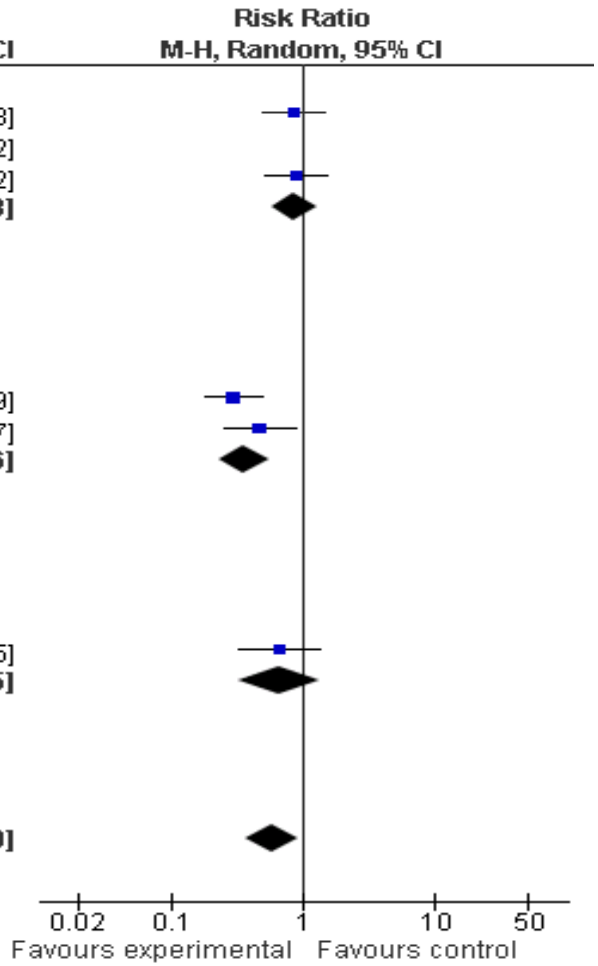
Heterogeneity: Tau² = 0.29; Chi² = 3.52, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.09 (P = 0.28)



H.6.3 Therapeutic footwear vs standard care for prevention of diabetic foot problems amongst high risk patients:

Rate of ulceration (different types of footwear vs standard care)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.2.1 Off the shelf insoles						
Reiber 2002	17	119	27	160	20.6%	0.85 [0.48, 1.48]
Reiber 2002	18	121	17	119	0.0%	1.04 [0.56, 1.92]
Reiber 2002	18	121	27	160	20.9%	0.88 [0.51, 1.52]
Subtotal (95% CI)		**240**		**320**	**41.5%**	**0.86 [0.58, 1.28]**
Total events	35		54			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.46)						
9.2.2 Bespoke orthoses						
Rizzo 2012	17	148	58	150	22.3%	0.30 [0.18, 0.49]
Uccioli 1995	9	33	21	36	19.1%	0.47 [0.25, 0.87]
Subtotal (95% CI)		**181**		**186**	**41.4%**	**0.36 [0.23, 0.56]**
Total events	26		79			
Heterogeneity: Tau² = 0.02; Chi² = 1.29, df = 1 (P = 0.26); I² = 23%						
Test for overall effect: Z = 4.55 (P < 0.00001)						
9.2.3 Therapeutic shoes + education						
Cisneros 2010	8	21	8	14	17.2%	0.67 [0.33, 1.35]
Subtotal (95% CI)		**21**		**14**	**17.2%**	**0.67 [0.33, 1.35]**
Total events	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)		**442**		**520**	**100.0%**	**0.58 [0.37, 0.90]**
Total events	69		141			
Heterogeneity: Tau² = 0.17; Chi² = 11.77, df = 4 (P = 0.02); I² = 66%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Test for subgroup differences: Chi² = 8.67, df = 2 (P = 0.01), I² = 76.9%						

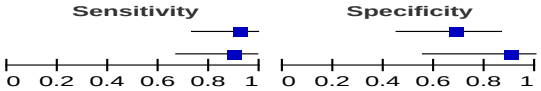


H.7 Review question 6 data analysis

H.7.1 ESR testing for osteomyelitis

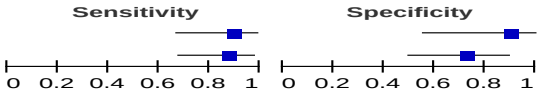
ERS≥60mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ertugrul 2009-ERS≥60	22	7	2	15	0.92 [0.73, 0.99]	0.68 [0.45, 0.86]
Kaleta 2001-ERS≥60	17	1	2	9	0.89 [0.67, 0.99]	0.90 [0.55, 1.00]



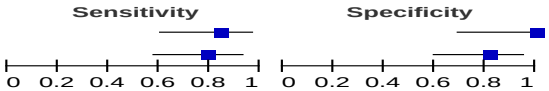
ERS≥65mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaleta 2001-ERS≥65	17	1	2	9	0.89 [0.67, 0.99]	0.90 [0.55, 1.00]
Ertugrul 2009-ERS≥65	21	6	3	16	0.88 [0.68, 0.97]	0.73 [0.50, 0.89]



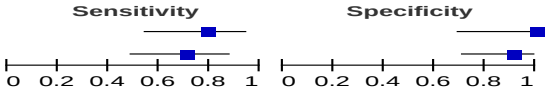
ERS≥75mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaleta 2001-ERS≥75	16	0	3	10	0.84 [0.60, 0.97]	1.00 [0.69, 1.00]
Ertugrul 2009-ERS≥75	19	4	5	18	0.79 [0.58, 0.93]	0.82 [0.60, 0.95]



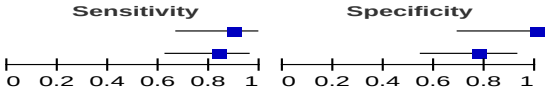
ERS≥80mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaleta 2001-ERS≥80	15	0	4	10	0.79 [0.54, 0.94]	1.00 [0.69, 1.00]
Ertugrul 2009-ERS≥80	17	2	7	20	0.71 [0.49, 0.87]	0.91 [0.71, 0.99]



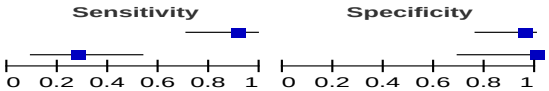
ERS≥70mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaleta 2001-ERS≥70	17	0	2	10	0.89 [0.67, 0.99]	1.00 [0.69, 1.00]
Ertugrul 2009-ERS≥70	20	5	4	17	0.83 [0.63, 0.95]	0.77 [0.55, 0.92]



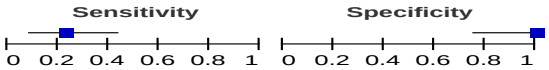
ERS>70mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Malabu 2007-ERS>70	20	1	2	20	0.91 [0.71, 0.99]	0.95 [0.76, 1.00]
Newman 1991-ERS>70	5	0	13	10	0.28 [0.10, 0.53]	1.00 [0.69, 1.00]



ERS>100mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Newman 1991-ERS>100	6	0	20	13	0.23 [0.09, 0.44]	1.00 [0.75, 1.00]



H.8 No meta-analysis performed for this question

No additional data analysis performed for this question

H.9 No meta-analysis performed for this question

No additional data analysis performed for this question

H.10 Review question 10 data analysis

Figure 1: Collagen dressings- complete wound healing

Study or Subgroup	Collagen dressing Events	Collagen dressing Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gottrup 2013	12	23	4	13	10.0%	1.70 [0.69, 4.19]
Veves 2002	51	104	39	84	90.0%	1.06 [0.78, 1.43]
Total (95% CI)		**127**		**97**	**100.0%**	**1.11 [0.83, 1.47]**
Total events	63		43			

Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)

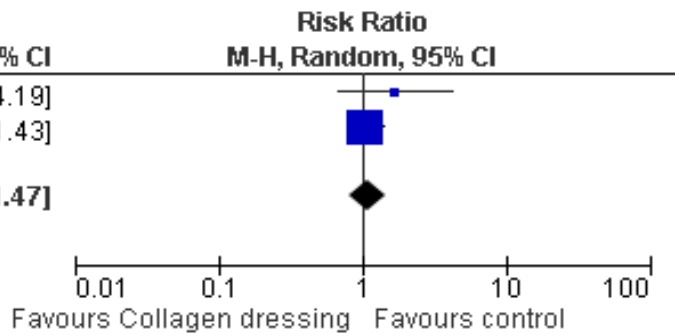


Figure 2: Collagen dressings- Adverse events

Study or Subgroup	Collagen dressing Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gottrup 2013	0	23	5	13	33.5%	0.05 [0.00, 0.89]
Veves 2002	25	104	35	84	66.5%	0.58 [0.38, 0.88]
Total (95% CI)		**127**		**97**	**100.0%**	**0.26 [0.03, 2.56]**
Total events	25		40			

Heterogeneity: Tau² = 2.00; Chi² = 2.89, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 1.16 (P = 0.25)

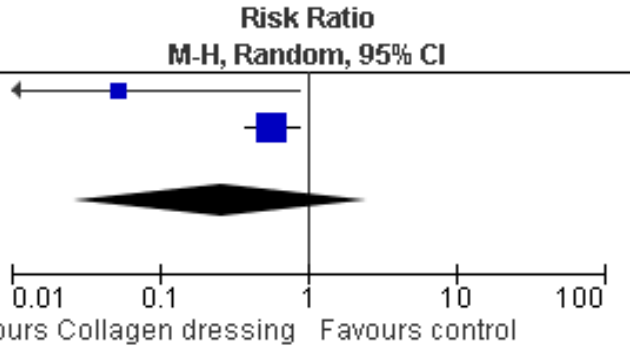


Figure 3: Irremovable versus removable offloading devices- Wound healing TCC versus Removable cast walker

Study or Subgroup	TCC Events	Total	RCW Events	Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
Armstrong 2001	17	19	13	20	15.5%	0.30 [0.07, 1.27]
Armstrong 2005	19	23	14	27	33.2%	0.36 [0.14, 0.96]
Faglia 2010	17	23	16	22	33.5%	0.96 [0.36, 2.52]
Gutekunst 2011	9	11	5	12	17.8%	0.31 [0.08, 1.19]
Total (95% CI)		**76**		**81**	**100.0%**	**0.47 [0.27, 0.84]**
Total events	62		48			

Heterogeneity: Tau² = 0.01; Chi² = 3.10, df = 3 (P = 0.38); I² = 3%
Test for overall effect: Z = 2.55 (P = 0.01)

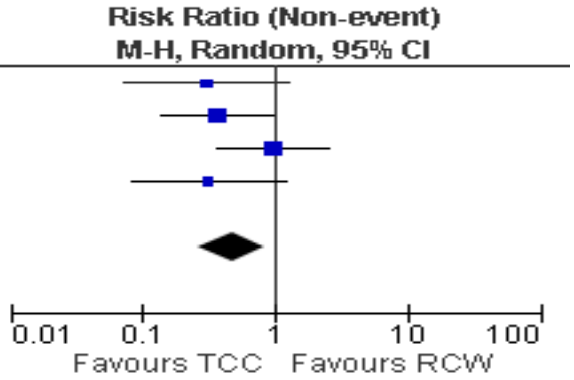


Figure 4: Irremovable versus removable offloading devices- Mean healing time (days) TCC versus Removable cast walker

Study or Subgroup	TCC Mean	TCC SD	TCC Total	RCW Mean	RCW SD	RCW Total	Weight	Std. Mean Difference IV, Random, 95% CI
Armstrong 2001	33.5	5.9	19	50.4	7.2	20	32.3%	-2.51 [-3.37, -1.65]
Armstrong 2005	41.6	18.7	23	58	15.2	27	35.0%	-0.96 [-1.54, -0.37]
Gutekunst 2011	95	61	11	94	64	12	32.7%	0.02 [-0.80, 0.83]
Total (95% CI)			**53**			**59**	**100.0%**	**-1.14 [-2.43, 0.15]**

Heterogeneity: Tau² = 1.14; Chi² = 17.66, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 1.74 (P = 0.08)

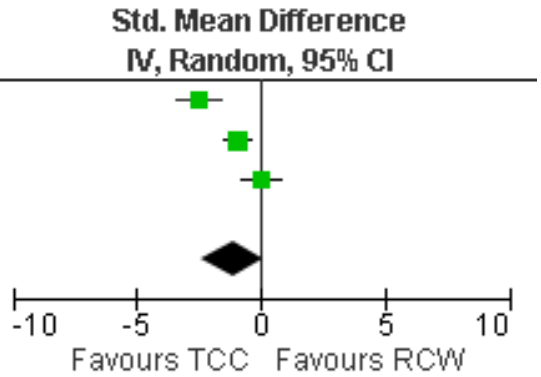


Figure 5: Irremovable versus removable offloading devices- Wound healing TCC versus Removable footwear

Study or Subgroup	Cast Events	Cast Total	Footwear Events	Footwear Total	Weight	Risk Ratio M-H, Random, 95% CI
Caravaggi 2010	13	26	5	24	52.1%	2.40 [1.01, 5.73]
Van de Weg 2008	6	23	6	20	47.9%	0.87 [0.33, 2.27]
Total (95% CI)		**49**		**44**	**100.0%**	**1.48 [0.55, 3.99]**
Total events	19		11			

Heterogeneity: Tau² = 0.30; Chi² = 2.37, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.77 (P = 0.44)

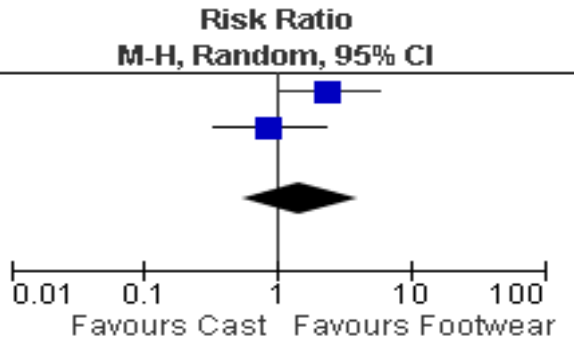


Figure 6: Irremovable versus Irremovable offloading devices- Wound healing TCC versus iTCC

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Katz 2005	15	20	17	21	29.8%	0.93 [0.67, 1.29]
Piaggesi 2007	19	20	17	20	70.2%	1.12 [0.91, 1.38]
Total (95% CI)		**40**		**41**	**100.0%**	**1.06 [0.88, 1.27]**
Total events	34		34			

Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 0.60 (P = 0.55)

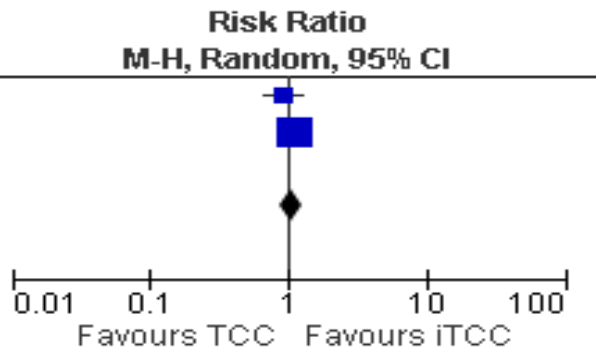
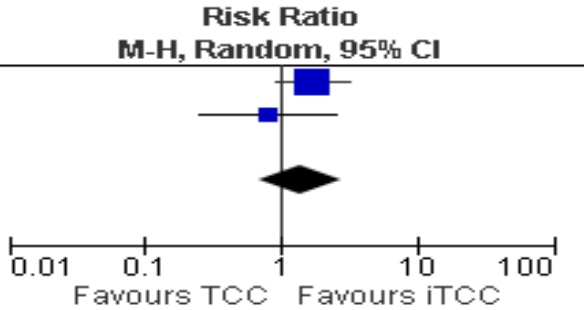


Figure 7: Irremovable versus Irremovable offloading devices- adverse events TCC versus iTCC

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Katz 2005	13	20	8	21	70.7%	1.71 [0.91, 3.21]
Piaggesi 2007	4	20	5	20	29.3%	0.80 [0.25, 2.55]
Total (95% CI)		**40**		**41**	**100.0%**	**1.37 [0.69, 2.72]**
Total events	17		13			

Heterogeneity: Tau² = 0.07; Chi² = 1.31, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 0.89 (P = 0.37)



H.11 Review question 11 data analysis

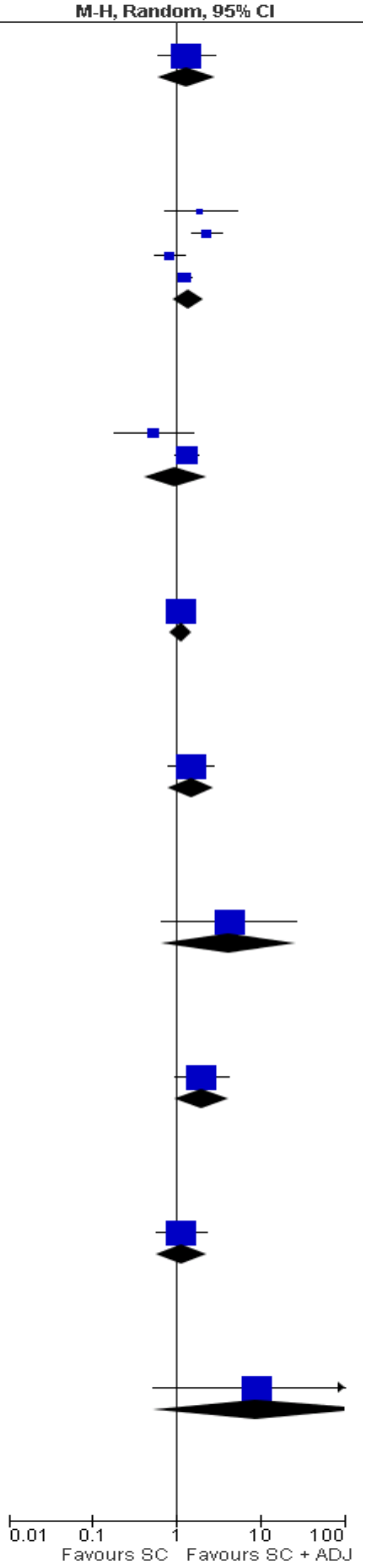
No additional data analysis performed for this question

H.12 Review question 12 data analysis

H.12.1 Cure rate

H.12.1.1 Growth factor and growth factor derived treatments

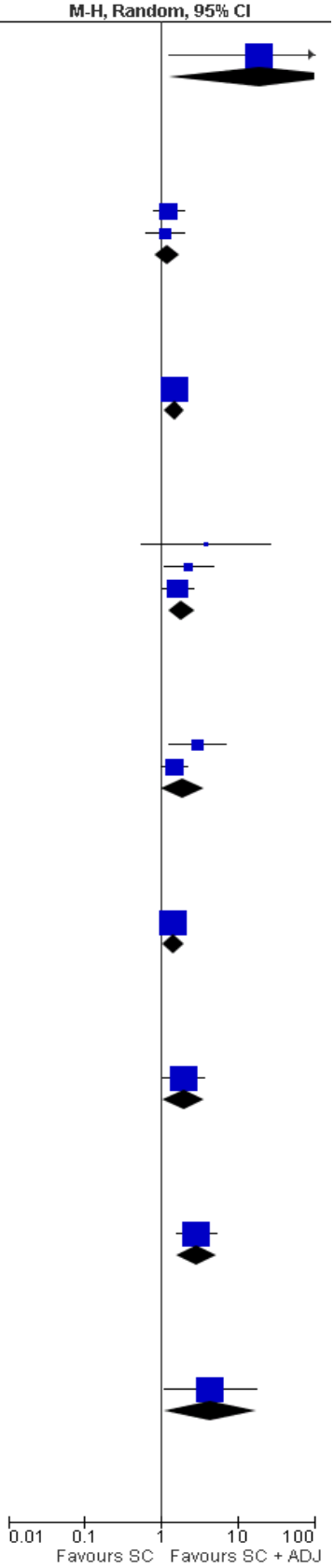
Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 GAM501 growth fact						
Blume 2011	27	66	5	16	100.0%	1.31 [0.60, 2.86]
Subtotal (95% CI)		**66**		**16**	**100.0%**	**1.31 [0.60, 2.86]**
Total events	27		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
2.1.2 Platelet growth fact						
AGRAWAL 2009	9	14	3	9	11.8%	1.93 [0.71, 5.26]
Hardikar 2005	39	55	18	58	26.8%	2.28 [1.50, 3.48]
Jaiswal 2010	15	25	18	25	27.3%	0.83 [0.56, 1.25]
Robson 2005	245	552	93	259	34.1%	1.24 [1.02, 1.49]
Subtotal (95% CI)		**646**		**351**	**100.0%**	**1.38 [0.91, 2.10]**
Total events	308		132			
Heterogeneity: Tau² = 0.13; Chi² = 12.60, df = 3 (P = 0.006); I² = 76%						
Test for overall effect: Z = 1.50 (P = 0.13)						
2.1.3 Fibroblast growth fact						
Richard 1995	3	9	5	8	33.9%	0.53 [0.18, 1.55]
Uchi 2009	57	92	22	47	66.1%	1.32 [0.94, 1.87]
Subtotal (95% CI)		**101**		**55**	**100.0%**	**0.97 [0.42, 2.26]**
Total events	60		27			
Heterogeneity: Tau² = 0.25; Chi² = 2.52, df = 1 (P = 0.11); I² = 60%						
Test for overall effect: Z = 0.06 (P = 0.95)						
2.1.4 B2 growth fact						
Robson 1999	77	131	24	46	100.0%	1.13 [0.82, 1.54]
Subtotal (95% CI)		**131**		**46**	**100.0%**	**1.13 [0.82, 1.54]**
Total events	77		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
2.1.5 VEGF growth fact						
Hanft 2008	15	29	9	26	100.0%	1.49 [0.79, 2.82]
Subtotal (95% CI)		**29**		**26**	**100.0%**	**1.49 [0.79, 2.82]**
Total events	15		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.21)						
2.1.6 CT-102 growth fact						
Steed 1992	5	7	1	6	100.0%	4.29 [0.67, 27.24]
Subtotal (95% CI)		**7**		**6**	**100.0%**	**4.29 [0.67, 27.24]**
Total events	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
2.1.7 Incretin						
marfella 2012	16	53	8	53	100.0%	2.00 [0.94, 4.27]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**2.00 [0.94, 4.27]**
Total events	16		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						
2.1.8 autologous platelet-rich plasma gel						
Driver 2006	13	40	9	32	100.0%	1.16 [0.57, 2.35]
Subtotal (95% CI)		**40**		**32**	**100.0%**	**1.16 [0.57, 2.35]**
Total events	13		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
2.1.38 rhEGF						
GOMEZ-VILLA 2014	4	17	0	17	100.0%	9.00 [0.52, 155.24]
Subtotal (95% CI)		**17**		**17**	**100.0%**	**9.00 [0.52, 155.24]**
Total events	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						



Test for subgroup differences: Chi² = 6.24, df = 8 (P = 0.62), I² = 0%

H.12.1.2 Dermal or skin substitutes

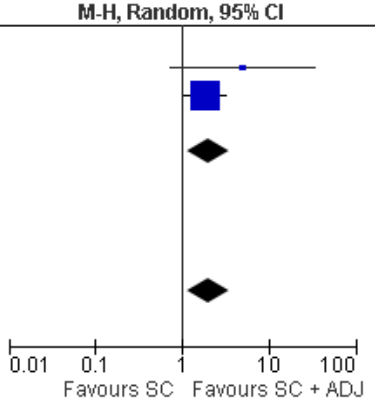
Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.9 Amniotic Membrane Wound Graft						
Zelen 2013	10	13	0	12	100.0%	19.50 [1.27, 300.42]
Subtotal (95% CI)		**13**		**12**	**100.0%**	**19.50 [1.27, 300.42]**
Total events	10		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.13 (P = 0.03)						
2.2.10 Hyalograft-3D followed by Laserskin autograft						
Caravaggi 2003	22	35	13	26	61.0%	1.26 [0.79, 1.99]
Uccioli 2011	19	80	17	80	39.0%	1.12 [0.63, 1.99]
Subtotal (95% CI)		**115**		**106**	**100.0%**	**1.20 [0.84, 1.72]**
Total events	41		30			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
2.2.12 Graftskin						
Veves 2001	63	112	36	96	100.0%	1.50 [1.11, 2.04]
Subtotal (95% CI)		**112**		**96**	**100.0%**	**1.50 [1.11, 2.04]**
Total events	63		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.60 (P = 0.009)						
2.2.13 Dermagraft						
Gentzkow 1996	11	37	1	13	4.0%	3.86 [0.55, 27.09]
Hanft 2002	15	24	6	22	26.9%	2.29 [1.08, 4.85]
Marston 2003	39	130	21	115	69.1%	1.64 [1.03, 2.62]
Subtotal (95% CI)		**191**		**150**	**100.0%**	**1.86 [1.26, 2.74]**
Total events	65		28			
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 3.13 (P = 0.002)						
2.2.14 GraftJacket						
Brigido 2006	12	14	4	14	34.4%	3.00 [1.28, 7.06]
Reyzelman 2009	32	46	18	39	65.6%	1.51 [1.02, 2.22]
Subtotal (95% CI)		**60**		**53**	**100.0%**	**1.91 [1.00, 3.65]**
Total events	44		22			
Heterogeneity: Tau² = 0.13; Chi² = 2.10, df = 1 (P = 0.15); I² = 52%						
Test for overall effect: Z = 1.96 (P = 0.05)						
2.2.15 Cultured Allogeneic Keratinocyte Sheet						
You 2012	23	27	19	32	100.0%	1.43 [1.03, 1.99]
Subtotal (95% CI)		**27**		**32**	**100.0%**	**1.43 [1.03, 1.99]**
Total events	23		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.16 (P = 0.03)						
2.2.16 Apligraf						
Edmonds 2009	17	33	10	38	100.0%	1.96 [1.05, 3.66]
Subtotal (95% CI)		**33**		**38**	**100.0%**	**1.96 [1.05, 3.66]**
Total events	17		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.10 (P = 0.04)						
2.2.17 Grafix						
LAVERY 2014	31	50	10	47	100.0%	2.91 [1.61, 5.26]
Subtotal (95% CI)		**50**		**47**	**100.0%**	**2.91 [1.61, 5.26]**
Total events	31		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.55 (P = 0.0004)						
2.2.18 RGD peptide matrix						
Steed 1995	14	40	2	25	100.0%	4.38 [1.08, 17.65]
Subtotal (95% CI)		**40**		**25**	**100.0%**	**4.38 [1.08, 17.65]**
Total events	14		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.07 (P = 0.04)						



Test for subgroup differences: Chi² = 13.43, df = 8 (P = 0.10), I² = 40.4%

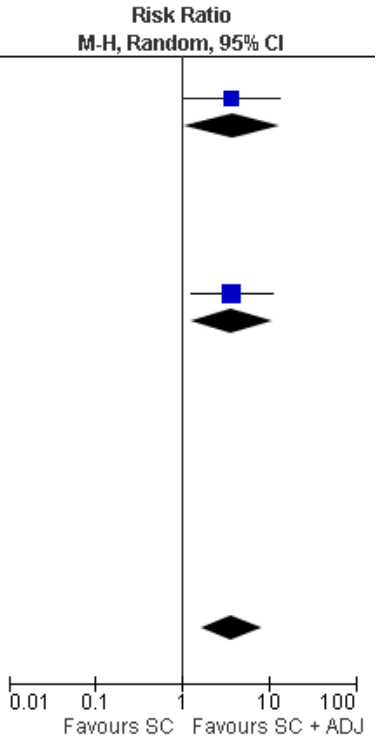
H.12.1.3 Hyperbaric oxygen therapy

Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.27 Hyperbaric oxygen therapy						
Abidia 2003	5	8	1	8	8.2%	5.00 [0.74, 33.78]
Londahl 2010	25	48	12	42	91.8%	1.82 [1.05, 3.16]
Ma 2013	0	8	0	8		Not estimable
Subtotal (95% CI)		**64**		**58**	**100.0%**	**1.98 [1.14, 3.43]**
Total events	30		13			
Heterogeneity: Tau² = 0.01; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%						
Test for overall effect: Z = 2.44 (P = 0.01)						
Total (95% CI)		**64**		**58**	**100.0%**	**1.98 [1.14, 3.43]**
Total events	30		13			
Heterogeneity: Tau² = 0.01; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%						
Test for overall effect: Z = 2.44 (P = 0.01)						
Test for subgroup differences: Not applicable						



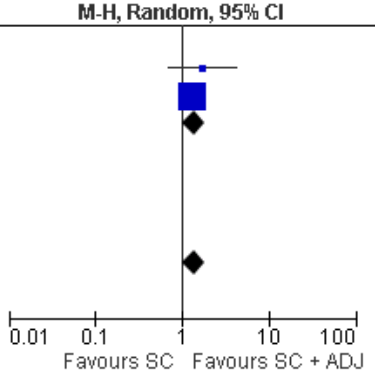
H.12.1.4 ANGIPARS herbal

Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.24 ANGIPARS herbal (oral)						
Bahrami 2008	5	6	2	9	42.4%	3.75 [1.05, 13.40]
Subtotal (95% CI)		**6**		**9**	**42.4%**	**3.75 [1.05, 13.40]**
Total events	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.03 (P = 0.04)						
2.3.25 ANGIPARS herbal (oral and topical)						
Bahrami 2008	6	6	2	9	57.6%	3.71 [1.25, 11.08]
Subtotal (95% CI)		**6**		**9**	**57.6%**	**3.71 [1.25, 11.08]**
Total events	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.35 (P = 0.02)						
2.3.26 ANGIPARS (intravenous)						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**12**		**18**	**100.0%**	**3.73 [1.63, 8.55]**
Total events	11		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 3.11 (P = 0.002)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						



H.12.1.5 Promogran

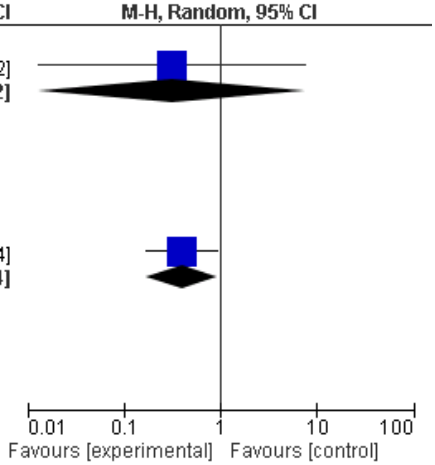
Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.34 Promogran						
Gottrup 2013	12	23	4	13	12.6%	1.70 [0.69, 4.19]
Veves 2002	51	138	39	138	87.4%	1.31 [0.93, 1.84]
Subtotal (95% CI)		**161**		**151**	**100.0%**	**1.35 [0.98, 1.86]**
Total events	63		43			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Total (95% CI)		**161**		**151**	**100.0%**	**1.35 [0.98, 1.86]**
Total events	63		43			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Not applicable						



H.12.2 Amputation rate

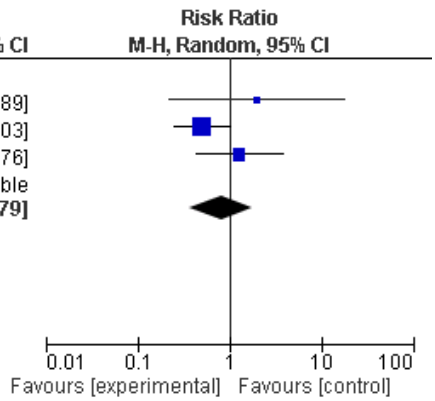
H.12.2.1 Dermal or skin substitutes

Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Grafix						
LAVERY 2014	0	50	1	47	100.0%	0.31 [0.01, 7.52]
Subtotal (95% CI)		**50**		**47**	**100.0%**	**0.31 [0.01, 7.52]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
2.6.12 Graftskin						
Veves 2001	7	112	15	96	100.0%	0.40 [0.17, 0.94]
Subtotal (95% CI)		**112**		**96**	**100.0%**	**0.40 [0.17, 0.94]**
Total events	7		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.10 (P = 0.04)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



H.12.2.2 Hyperbaric oxygen therapy

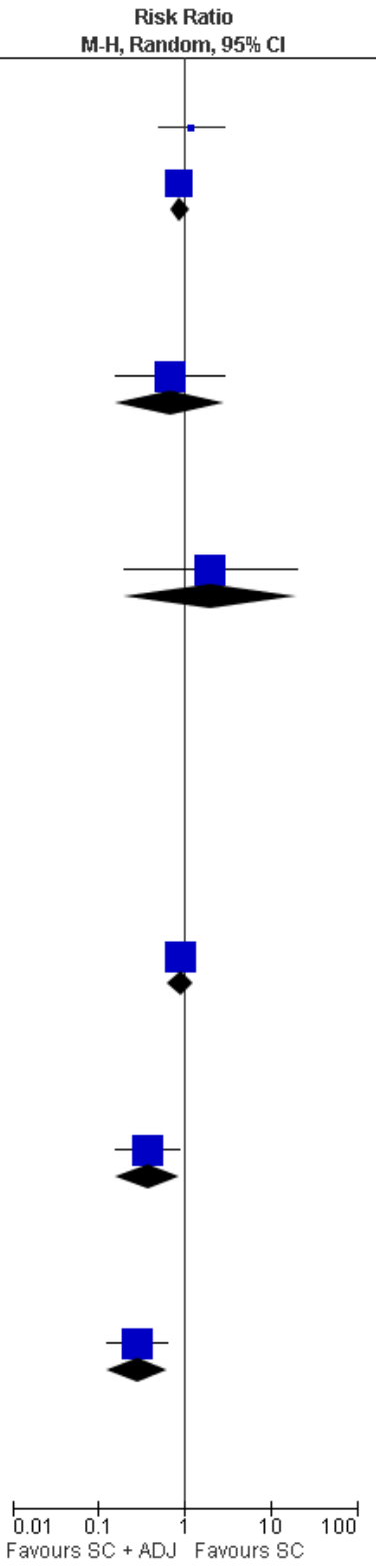
Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.27 Hyperbaric oxygen therapy						
Abidia 2003	2	8	1	8	11.4%	2.00 [0.22, 17.89]
Faglia 1996	8	35	15	33	54.0%	0.50 [0.25, 1.03]
Londahl 2010	7	49	5	45	34.6%	1.29 [0.44, 3.76]
Ma 2013	0	8	0	8		Not estimable
Subtotal (95% CI)		**100**		**94**	**100.0%**	**0.81 [0.37, 1.79]**
Total events	17		21			
Heterogeneity: Tau² = 0.16; Chi² = 2.95, df = 2 (P = 0.23); I² = 32%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Not applicable						



H.12.3 Adverse events rate

H.12.3.1 Growth factor and growth factor derived treatments

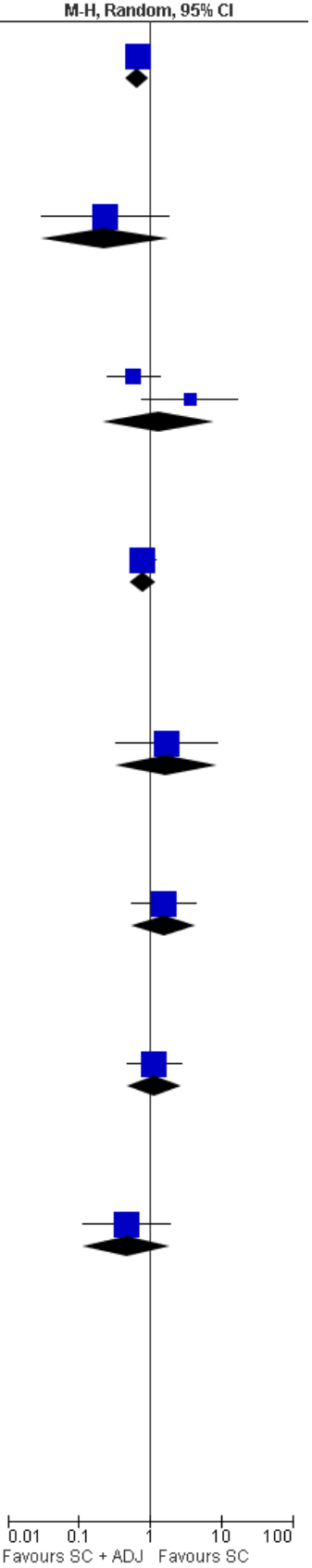
Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Platelet						
Bhansali 2009	0	10	0	10		Not estimable
Hardikar 2005	9	55	8	58	9.6%	1.19 [0.49, 2.85]
Jaiswal 2010	0	25	0	25		Not estimable
Robson 2005	98	407	53	190	90.4%	0.86 [0.65, 1.15]
Subtotal (95% CI)		**497**		**283**	**100.0%**	**0.89 [0.68, 1.17]**
Total events	107		61			
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
2.8.3 Fibroblast						
Uchi 2009	4	92	3	47	100.0%	0.68 [0.16, 2.92]
Subtotal (95% CI)		**92**		**47**	**100.0%**	**0.68 [0.16, 2.92]**
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.61)						
2.8.4 rhEGF						
GOMEZ-VILLA 2014	2	17	1	17	100.0%	2.00 [0.20, 20.04]
Subtotal (95% CI)		**17**		**17**	**100.0%**	**2.00 [0.20, 20.04]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
2.8.5 GAM501						
Blume 2011	0	66	0	16		Not estimable
Subtotal (95% CI)		**66**		**16**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.8.6 VEGF						
Hanft 2008	19	29	19	26	100.0%	0.90 [0.63, 1.28]
Subtotal (95% CI)		**29**		**26**	**100.0%**	**0.90 [0.63, 1.28]**
Total events	19		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.8.7 Incretin						
marfella 2012	6	53	16	53	100.0%	0.38 [0.16, 0.88]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**0.38 [0.16, 0.88]**
Total events	6		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.24 (P = 0.02)						
2.8.8 autologous platelet-rich plasma gel						
Driver 2006	6	40	17	32	100.0%	0.28 [0.13, 0.63]
Subtotal (95% CI)		**40**		**32**	**100.0%**	**0.28 [0.13, 0.63]**
Total events	6		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.07 (P = 0.002)						



Test for subgroup differences: Chi² = 11.05, df = 5 (P = 0.05), I² = 54.7%

H.12.3.2 Dermal or skin substitutes

Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.8 Grafix						
LAVERY 2014	22	50	31	47	100.0%	0.67 [0.46, 0.97]
Subtotal (95% CI)		**50**		**47**	**100.0%**	**0.67 [0.46, 0.97]**
Total events	22		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						
2.9.9 Amniotic Membrane Wound Graft						
Zelen 2013	1	13	4	12	100.0%	0.23 [0.03, 1.79]
Subtotal (95% CI)		**13**		**12**	**100.0%**	**0.23 [0.03, 1.79]**
Total events	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
2.9.10 Hyalograft-3D followed by Laserskin autograft						
Caravaggi 2003	7	43	10	36	56.2%	0.59 [0.25, 1.38]
Uccioli 2011	7	84	2	87	43.8%	3.63 [0.78, 16.95]
Subtotal (95% CI)		**127**		**123**	**100.0%**	**1.30 [0.21, 7.93]**
Total events	14		12			
Heterogeneity: Tau² = 1.32; Chi² = 4.25, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 0.29 (P = 0.77)						
2.9.13 Dermagraft						
Hanft 2002	14	24	16	22	100.0%	0.80 [0.52, 1.23]
Subtotal (95% CI)		**24**		**22**	**100.0%**	**0.80 [0.52, 1.23]**
Total events	14		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
2.9.14 GraftJacket						
Brigido 2004	0	20	0	20		Not estimable
Reyzelman 2009	4	46	2	39	100.0%	1.70 [0.33, 8.77]
Subtotal (95% CI)		**66**		**59**	**100.0%**	**1.70 [0.33, 8.77]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
2.9.15 Cultured Allogeneic Keratinocyte Sheet						
You 2012	6	20	5	26	100.0%	1.56 [0.55, 4.39]
Subtotal (95% CI)		**20**		**26**	**100.0%**	**1.56 [0.55, 4.39]**
Total events	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
2.9.16 Apligraf						
Edmonds 2009	8	33	8	38	100.0%	1.15 [0.49, 2.73]
Subtotal (95% CI)		**33**		**38**	**100.0%**	**1.15 [0.49, 2.73]**
Total events	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
2.9.17 RGD peptide matrix						
Steed 1995	3	40	4	25	100.0%	0.47 [0.11, 1.92]
Subtotal (95% CI)		**40**		**25**	**100.0%**	**0.47 [0.11, 1.92]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
2.9.22 Processed lipoaspirate cells						
Han 2010	0	26	0	26		Not estimable
Subtotal (95% CI)		**26**		**26**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

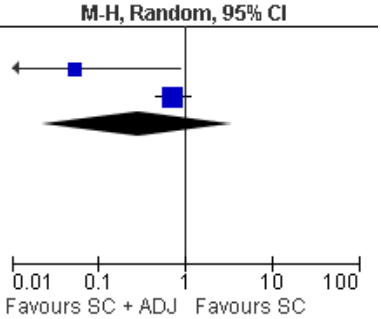


Test for subgroup differences: Chi² = 6.23, df = 7 (P = 0.51), I² = 0%

H.12.3.3 Promogran

Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.11.36 Promogran						
Gottrup 2013	0	23	5	13	35.9%	0.05 [0.00, 0.89]
Veves 2002	25	138	35	138	64.1%	0.71 [0.45, 1.13]
Subtotal (95% CI)		**161**		**151**	**100.0%**	**0.28 [0.02, 3.48]**
Total events	25		40			

Heterogeneity: Tau² = 2.52; Chi² = 3.38, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.99 (P = 0.32)



Test for subgroup differences: Not applicable

H.12.4 Infection rate

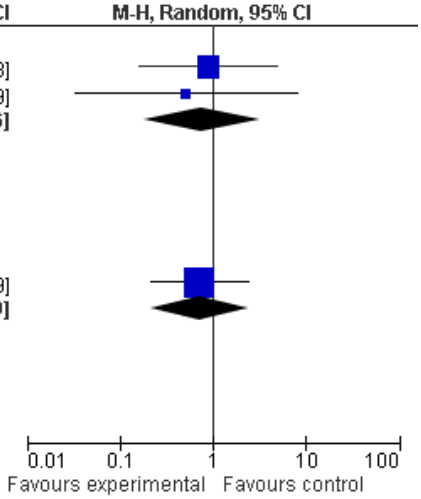
H.12.4.1 Growth factor and growth factor derived treatments

Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.12.3 Fibroblast						
Richard 1995	2	9	2	8	72.0%	0.89 [0.16, 4.93]
Uchi 2009	1	92	1	47	28.0%	0.51 [0.03, 7.99]
Subtotal (95% CI)		**101**		**55**	**100.0%**	**0.76 [0.18, 3.26]**
Total events	3		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.12.6 VEGF						
Hanft 2008	4	29	5	26	100.0%	0.72 [0.22, 2.39]
Subtotal (95% CI)		**29**		**26**	**100.0%**	**0.72 [0.22, 2.39]**
Total events	4		5			

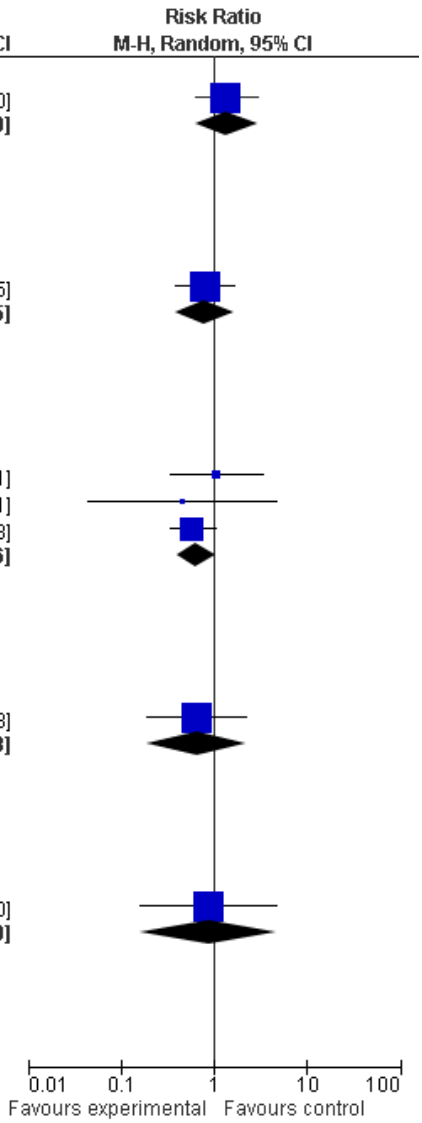
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%

H.12.4.2 Dermal or skin substitutes

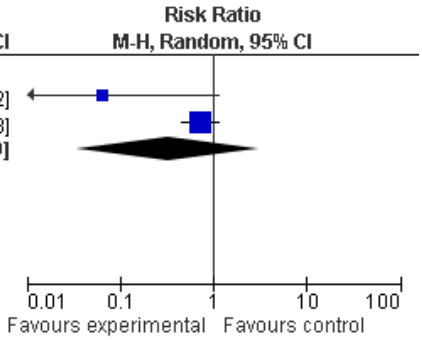
Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.13.10 Hyalograft-3D followed by Laserskin autograft						
Uccioli 2011	13	84	10	87	100.0%	1.35 [0.62, 2.90]
Subtotal (95% CI)		**84**		**87**	**100.0%**	**1.35 [0.62, 2.90]**
Total events	13		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
2.13.12 Graftskin						
Veves 2001	12	112	13	96	100.0%	0.79 [0.38, 1.65]
Subtotal (95% CI)		**112**		**96**	**100.0%**	**0.79 [0.38, 1.65]**
Total events	12		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
2.13.13 Dermagraft						
Gentzkow 1996	9	37	3	13	18.7%	1.05 [0.34, 3.31]
Hanft 2002	1	24	2	22	4.5%	0.46 [0.04, 4.71]
Marston 2003	17	163	27	151	76.8%	0.58 [0.33, 1.03]
Subtotal (95% CI)		**224**		**186**	**100.0%**	**0.64 [0.39, 1.06]**
Total events	27		32			
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.74 (P = 0.08)						
2.13.14 GraftJacket						
Brigido 2006	3	13	5	14	100.0%	0.65 [0.19, 2.18]
Subtotal (95% CI)		**13**		**14**	**100.0%**	**0.65 [0.19, 2.18]**
Total events	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
2.13.15 Cultured Allogeneic Keratinocyte Sheet						
You 2012	2	20	3	26	100.0%	0.87 [0.16, 4.70]
Subtotal (95% CI)		**20**		**26**	**100.0%**	**0.87 [0.16, 4.70]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						



Test for subgroup differences: Chi² = 2.62, df = 4 (P = 0.62), I² = 0%

H.12.4.3 Promogran

Study or Subgroup	SC + ADJ Events	SC + ADJ Total	SC Events	SC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.14.29 Promogran						
Gottrup 2013	0	23	4	13	32.9%	0.06 [0.00, 1.12]
Veves 2002	25	138	35	138	67.1%	0.71 [0.45, 1.13]
Subtotal (95% CI)		**161**		**151**	**100.0%**	**0.32 [0.03, 3.09]**
Total events	25		39			
Heterogeneity: Tau² = 1.92; Chi² = 2.77, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 0.98 (P = 0.33)						



Test for subgroup differences: Not applicable

H.13 Review question 13 data analysis

No additional data analysis performed for this question

H.14 Review question 14 data analysis

No additional data analysis performed for this question

H.15 Review question 15 data analysis

No additional data analysis performed for this question

H.16 Review question 16 data analysis

No additional data analysis performed for this question